REMARKS

Claims 1-26 are currently pending and under consideration.

Applicants have amended claims 1 and 2 to replace the term "prodrug or derivative" with the term "salt" to overcome the Examiner's rejections.

Applicants have amended claims 3, 5, and 7 to more clearly define "features" as "compound variables" to overcome the Examiner's rejections.

Applicants have amended claim 21 to correct a typographical error. Therein, applicants have deleted the inadvertent double recitation of the term "method of."

Applicants have cancelled claims 13, 14, 19, 20, 22, and 23.

Applicants have amended claims 15, 16, 17, 18, 21, 24, 25, and 26 and have added new claims 27-31 in light of the Examiner rejections.

None of these amendments add new matter.

Finally, all of these amendments and claim cancellations are specifically made without prejudice to applicants' ability to seek patents for the cancelled or non-elected subject matter.

The Office Action

35 U.S.C. § 112, second paragraph

1. Claims 1-26 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner asserts that recitation of "pharmaceutically acceptable derivative or prodrug thereof" in claim 1 is indefinite because it implies more than what is being positively recited. In an effort to expedite prosecution, applicants have amended claim 1 to instead recite "pharmaceutically acceptable salt thereof". Applicants respectfully submit that no new matter is presented with this amendment; rather, pharmaceutically acceptable salts are supported in the specification throughout (see page 23 line 29 to page 24 line 2). In view of the Amendment to claim 1, applicants respectfully request that the rejection of claims 1-26 is withdrawn.

2. The Examiner has rejected claims 5 and 7 under 35 U.S.C. § 112, second paragraph and asserts that it is not clear what is considered "features" in the recited groups therein to be selected. In an effort to expedite prosecution, applicants have amended claims 5 and 7 as well as claim 3, which also includes the term "features", to more clearly define "features" as "compound

variables" (e.g., Ring C, R^x, R^y, etc.). In view of the amendment to claims 3, 5, and 7 as detailed above, Applicants respectfully request that the Examiner withdraw the rejection under 35 U.S.C. § 112, second paragraph.

35 U.S.C. § 112, first paragraph

1. Claims 1-26 stand rejected under 35 U.S.C. § 112, first paragraph as lacking enablement. The Examiner contends that although the specification is enabling "for making salts of the claimed compounds," the specification is not enabling for derivatives or prodrugs of the compound (April 11, 2005 Office Action p. 4). Applicants have amended claims 1 and 2 to delete "derivative or prodrug" and substitute therefore "salt," thus obviating these rejections. Support for this amendment may be found in the specification throughout (see p. 23 line 29 to p. 24 line 2).

2. Claims 13-22 and 24-26 stand rejected under 35 U.S.C. § 112, first paragraph as lacking enablement. The Examiner contends that the specification "while being enabling for treating diabetes," does not reasonably provide enablement for treatment of any or all diseases including those yet to be linked with the various modes of action embraced by the claim language. The Examiner additionally states that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Applicants respectfully disagree with the Examiner and respectfully submit that the Examiner has not established a *prima facie* case of nonenablement. As detailed above, in an effort to expedite prosecution, Applicants have cancelled claims 13, 14, 19, 20, 22, and 23, amended claims 15, 16, 17, 18, 21, 24, 25 and 26, and added claims 27-31. Thus, the rejection under 35 U.S.C. § 112, first paragraph will be addressed for the amended and newly added claims. Applicants reserve the right, however, to pursue the subject matter from any amended or cancelled claims in future continuation or divisional applications.

The Examiner has rejected claim 12 which recites "A method of inhibiting Aurora-2 or GSK-3 activity in a biological sample comprising the step of contacting said biological sample with a compound according to any one of claims 1-9. Applicants respectfully submit that the Examiner has not established a *prima facie* case of nonenablement because the Examiner has not provided a reasonable explanation as to why the scope of protection provided by claim 12, which is directed to *a method of inhibiting Aurora-2 or GSK-3 activity in a biological sample* (and does

not recite methods for treating a disease, as the Examiner suggests in the rejection) is not adequately enabled by the description of the invention provided in the specification. Applicants have provided several examples on pages 311-315 of the specification of compounds that exhibit the ability to inhibit Aurora-2 or GSK-3 activity; however, the Examiner has not provided a reasonable explanation as to why the scope of protection provided by claim 12 (directed to a method of inhibiting Aurora-2 or GSK-3 activity) is not adequately enabled. Applicants thus respectfully request that the Examiner withdraw the rejection of claim 12.

The Examiner has rejected claims 15-26 because the instant claims are drawn to a method of treating a disease of various organs based on certain modes of action (e.g., inhibition of Aurora-2 or GSK-3), and states that these claims read on any or all diseases of these organs for which there is no enabling disclosure (other than for diabetes). In order to expedite prosecution, applicants have either amended or cancelled the rejected mechanism-dependant method of treatment claims and have replaced them with method of treatment claims which are not mechanism dependent, but instead recite specific diseases which are currently known to be correlated with Auora-2, GSK-3, phosphorylation of tau, or phosphorylation of ß-catenin.

The Examiner also contends that "many, if not most of the diseases such as Alzheimer's disease, multiple sclerosis, ALS, cancer, etc. are very difficult to treat and at present there is no known drug which can successfully reverse the course of these diseases." Applicants would like to point out that each of the rejected claims recites the *treatment* of certain disease states and does not recite the *reversal* of disease states, and thus the Examiners assertion that there is no known drug that can successfully reverse the course of the cited diseases does not apply to Applicant's claims. Applicants would like to point out that several drugs have been marketed for the treatment of Alzheimer's and cancer, for example, Aricept®, Gleevec® (which is also a kinase inhibitor), and Taxol®, to name a few.

The Examiner also contends that, "the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host". Applicants respectfully submit that the rejected claims are in fact enabled by the specification. As detailed below, inhibition of Auora-2, GSK-3, phosphorylation of Tau, and phosphorylation of ß-catenin have been correlated to the treatment of the claimed diseases.

The MPEP states, "if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the Examiner has evidence

that the model does not correlate." See MPEP § 2164.02. Only a "reasonable correlation" is required; the test does not have to be "highly predictive," as the Examiner suggests.

Correlation for the diseases and conditions recited in the rejected claims can be found throughout the specification as originally filed. For example, it has been shown that the phosphorylation of ß-catenin by GSK-3 is associated with increased neuronal cell death. Accordingly, the inhibition of GSK-3 is useful for treating neurological and neurodegenerative disorders. See page 5, lines 1-8. Furthermore, applicants respectfully point out that a well known characteristic of Alzheimer's disease relates to ß-amyloid peptide and the formation of intracellular neurofibrillary tangles caused by the abnormal phosphorylation of Tau protein. See page 4, lines 20-33. As disclosed in the background section of the specification, GSK-3 has been shown to play a key role in this abnormal phosphorylation of Tau protein in both *in vitro* and *in vivo* models. Id. Lovestone reports *in vitro* correlation by showing that both GSK-3a and GSK-3ß induce cellular phosphorylation of tau, and therefore are likely to be the enzymes that induce hyperphosphorylation of tau in Alzheimer's disease. See page 4 lines 20-33. Lovestone et al., *Current Biology* 4, 1077-86 (1994). Brownlees further reports correlation in *in vivo* models. Brownlees created transgenic mice with human GSK-3ß transgenes and was able to show *in vivo* tau phosphorylation by GSK-3ß in the brain. See page 4 lines 20-33. Brownlees et al., *Neuroreport* 8, 3251-55 (1997).

The Examiner asserts that no compound has ever been found to treat cancers of all types generally, and therefore, "proof must be provided that this revolutionary assertion has merits." (April 11, 2005 Office Action, p. 8) Applicants' compounds are applicable to cancer treatments generally. As would be recognized by skilled practitioners, some compounds may not be capable of treating cancer generally because of their mechanism of action. If a compound's mechanism of action is specific for a certain type of cancer, then that compound would not be useful for treating cancer generally. However, if a compound's mechanism of action is general for all cell types, then that compound could be used to treat cancer generally.

Aurora-2 inhibition is an example of a mechanism that is applicable to cancer generally. Aurora-2 kinases are involved in fundamental processes in cell division. Cell division is dependent on the function of Aurora-2 kinase. Aurora-2 activity is therefore essential for cell division. Accordingly, Aurora-2 inhibitors would inhibit cell division in all types of cells. Therefore, applicants' compounds could be used to treat cancer and, more specifically, the types of cancers recited in claim 16. Accordingly, applicants have enabled the treatment of different

types of cancers.

Although the Examiner asserts that the specification is not enabling for the treatment of the diverse disorders of the instant claims, applicants respectfully submit that the models that made up the state of the art at applicants' filing date do indeed correlate inhibition of Aurora-2, GSK-3, phosphorylation of Tau protein, and phosphorylation of ß-catenin with the treatment of the disorders of the instant claims.

The Examiner contends that factors such as claim breadth, "amount of direction or guidance present," and "the state of the prior art," are sufficiently lacking such that the "unpredictable nature of the art" renders the specification non-enabling for the claimed invention. Id at 9. Enablement requires an applicant to provide sufficient guidance so that one of skill in the art may use the invention. The MPEP states that "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." See MPEP § 2164.06. Applicants do in fact provide sufficient direction and guidance in their specification as originally filed. Specifically, applicants provide the tools to make the compounds of the instant invention (see, e.g., page 64, line 15 to page 68, line 12), to assess the activity of those compounds (see, e.g., page 68, line 15 to page 71, line 4), and to use the compounds (see, e.g., page 17, line 4 to page 27, line 3).

The Examiner has not provided evidence that there is no correlation between the inhibition of Aurora-2, GSK-3, phosphorylation of Tau protein, and phosphorylation of ß-catenin methods recited in claims 13-22 and 24-26. Accordingly, applicants respectfully submit that the Examiner has not established a *prima facie* case for non-enablement.

Because the references cited in the background section of the present application and those known in the art suggest a correlation between the inhibition of GSK-3 or Aurora-2 protein kinase with the treatment of diseases such as diabetes, cancer, Alzheimer's disease, schizophrenia, and CNS disorders; and because the Examiner has not provided evidence that there is no correlation between the Aurora-2, GSK-3, phosphorylation of Tau protein, and phosphorylation of ß-catenin and the treatment of diabetes, cancer, Alzheimer's disease, schizophrenia, and CNS disorders, Applicants respectfully submit that claims 13-22 and 24-31 (as newly amended) are indeed enabled. Accordingly, applicants respectfully request that the Examiner withdraw the rejection of claims 13-22 and 24-26 (and now applied to claims 13-22 and 24-31)

Applicants request entry of the above amendments, favorable consideration of the application, and early allowance of the pending claims.

Respectfully submitted,

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